PBDEs – Rising Levels in Fish, Tox Review and the California Ban

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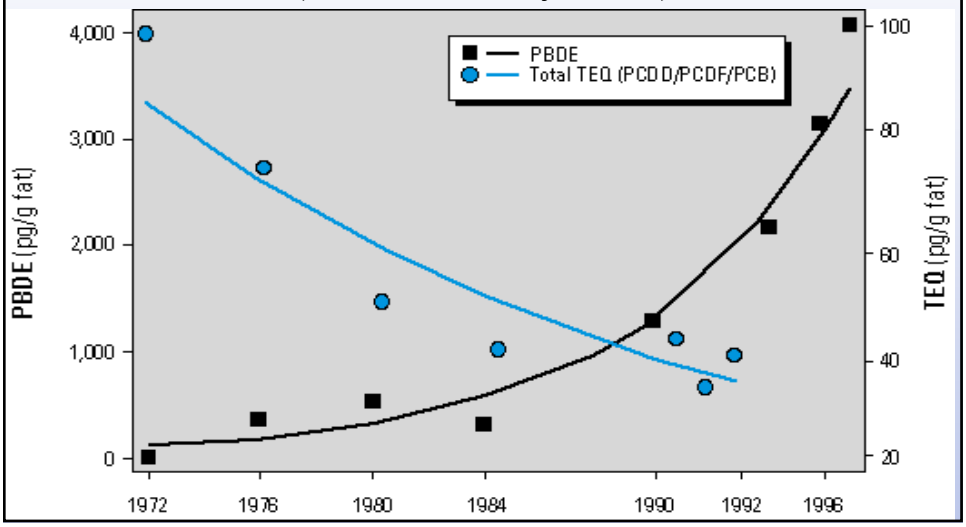
Office of Environmental Health Hazard Assessment

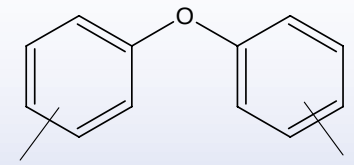
The figure that started it all for us in California . . .

Organohalogen Compounds in Human Milk in Sweden
(Norén and Mieronyté, 1998)



Introduction

The polybrominated dipenylethers (PBDEs)



- Added to many consumer products
- Flame retardant
- Saves lives

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PBDE Use in the Americas

PBDE Technical Mixture	Million lbs/yr (2001)	% of World's Use	Product Uses
Penta-BDE†	15.7	95	Furniture (foam cushions)
Octa-BDE	3.3	40	Electronics (ABS plastic, cable)
Deca-BDE	54.0	44	Electronics (HIPS plastic) and textiles

† Highly bioaccumulative

BSEF, 2003

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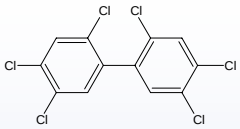
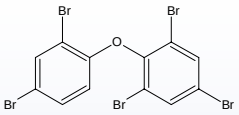
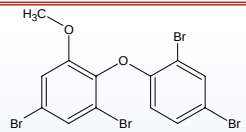
Structural Similarity of PBDEs, Their Metabolites and Environmental Derivatives to T4 and PCBs



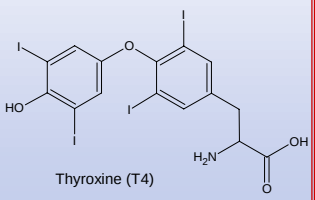
2,2',4,4',5,5'-hexachlorobiphenyl
(PCB-153)



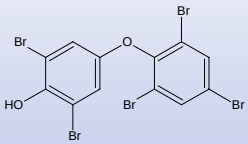
2,2',4,4',6-pentabromodiphenylether
(PBDE-100)



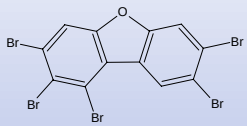
2-(2',4'-dibromophenoxy)-4,6-dibromoanisol
(methoxy-PBDE)



Thyroxine (T4)



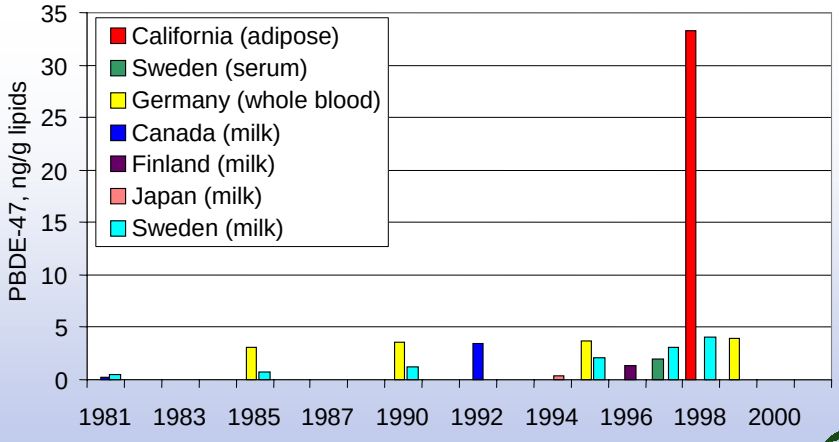
4-(2',4',6'-tribromophenoxy)-2,6-dibromophenol
(hydroxy-PBDE)



2,3,4,7,8-pentabromodibenzofuran
(PBDF)

The data that accelerated our efforts in CA . . . .

Lipid-normalized PBDE-47 (tetra)
in Human Tissues



CA data from She *et al.* (2002)

PBDEs Relate to Several Important Topics of the Day

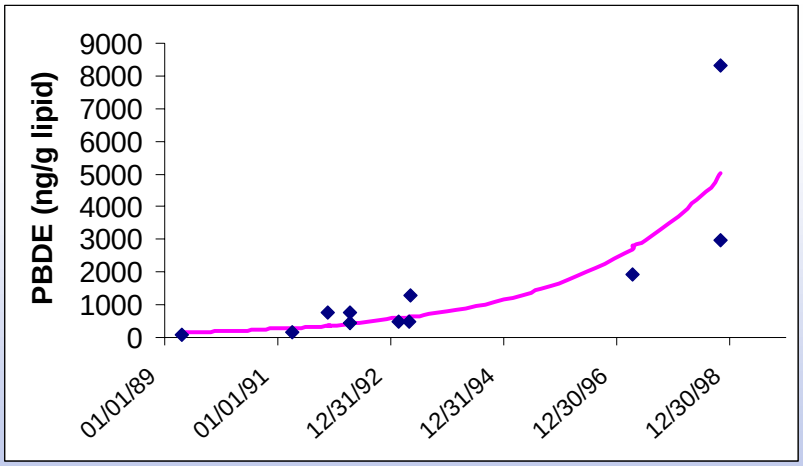
- **Children's Health**
- **Endocrine Disruption**
- **Persistent Organic Pollutants (POP)/ Persistent Bioaccumulative Toxicants (PBT)**
- **Emerging Environmental Challenge**
- **High Production Volume (HPV) Chemical**

PBDEs Have Become Ubiquitous Environment Contaminants

PBDEs are measured in

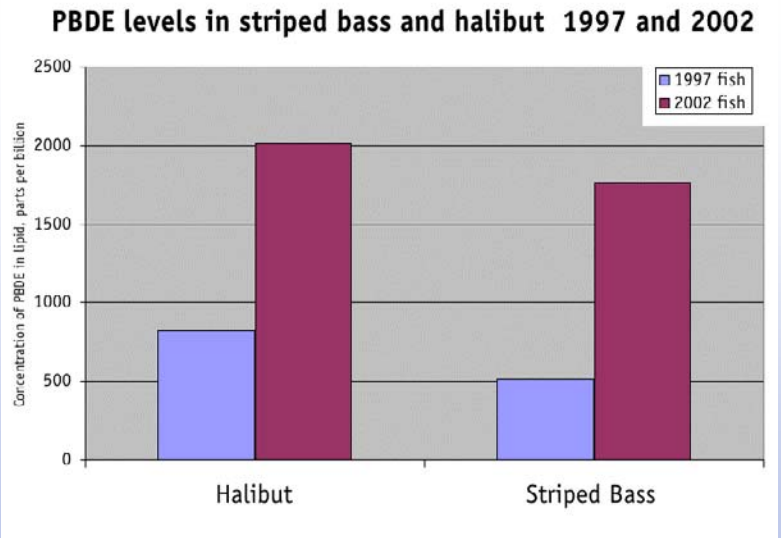
- Indoor and outdoor air
- Remote Arctic regions (i.e., long-range transport)
- House and office dust
- Rivers and lakes and sediments
- Sewage sludge
- Foods
- Biota (terrestrial and marine mammals, fish, humans)

Time-trend: PBDEs in Blubber of California Seals (She *et al.*, 2002)



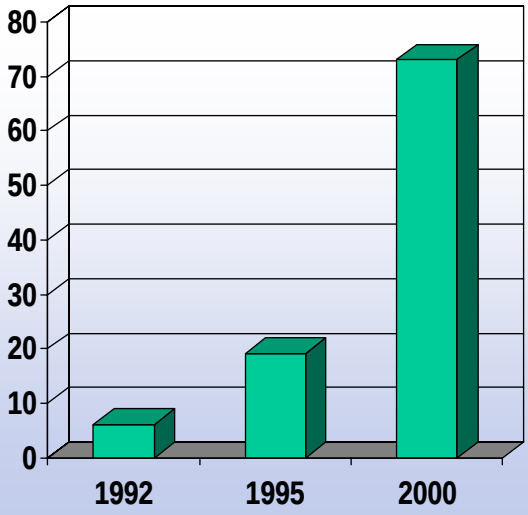
N=11

Fish from San Francisco Bay



EWG (2003)

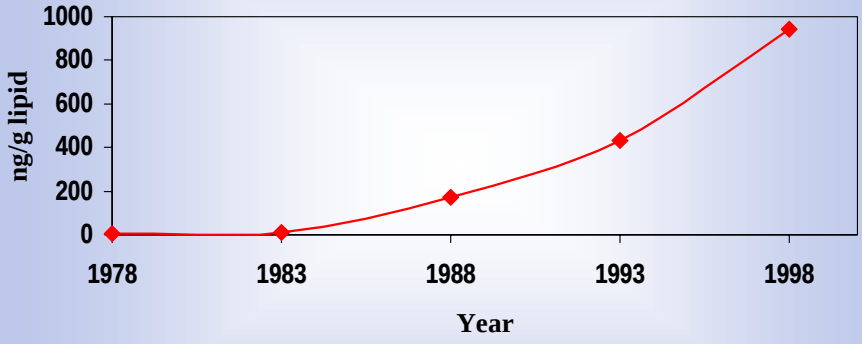
PBDEs in Columbia River Whitefish



From Genelle, British Columbia

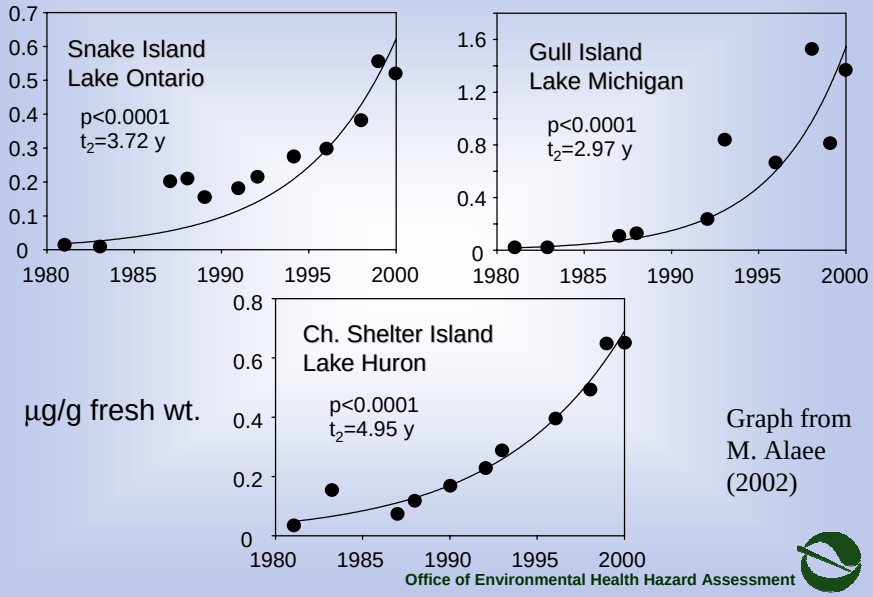
Rayne *et al.* (2003) Environ Sci Technol 37(13):2847-54.

PBDEs in Lake Ontario Trout (1978 - 1998)



Luross et al. (2000)

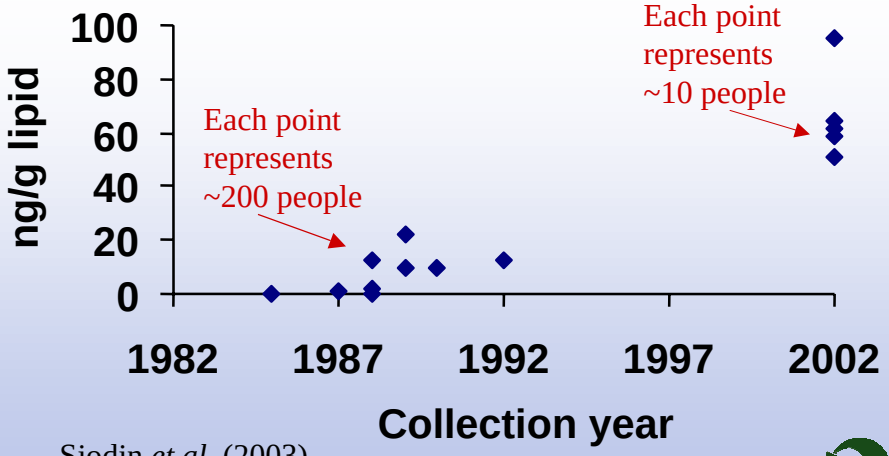
PBDEs in Herring Gull Eggs - Great Lakes



Graph from M. Alaee (2002)

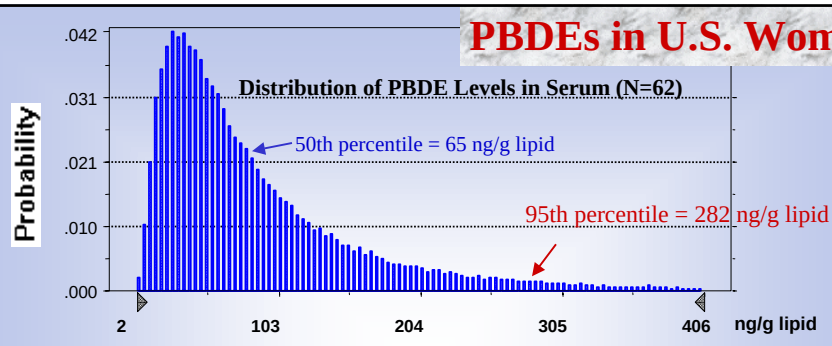
PBDE Levels Are Rising in U.S. Residents

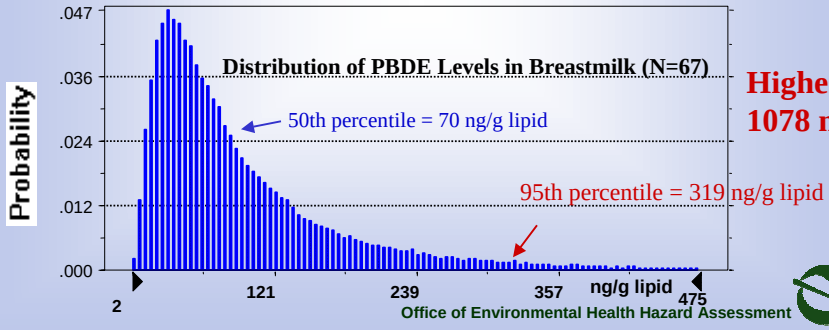
(Sum 7 PBDE Congeners in Serum)



Sjodin *et al.* (2003)

PBDEs in U.S. Women





Highest = 1078 ng/g

Data from Petreas *et al.*, 2003; Mazdai *et al.*, 2003; Schecter *et al.*, 2003; EWG, 2003

High-end Human Exposures

- **5% of people likely have lipid-normalized PBDE levels greater than 300 ng/g**
  - That's about 15 million people in the U.S.
- **WHY?**
  - Fish intake?
  - Indoor exposures, house dust?
  - Differences in pharmacokinetics (i.e., inter-individual variability in uptake, metabolism or excretion)?
  - Look for future research to address this question

For Many Individuals, PBDE Tissue Levels Have Now Surpassed PCB Levels

- **Initial data from our agency indicate that among 57 California women :**

7% had higher tissue concentrations of total PBDEs than total PCBs

Toxicity Concerns for the PBDEs

- **Endocrine disruption**
  - **Thyroid and estrogenic effects**
- **Developmental effects**
  - **Brain and reproductive organs**
- **Possibly cancer**
  - **NTP initiating long-term studies of Penta**
  - **Environmental conversion to dioxins/furans**
    - **Brominated dioxins/furans measured in people**

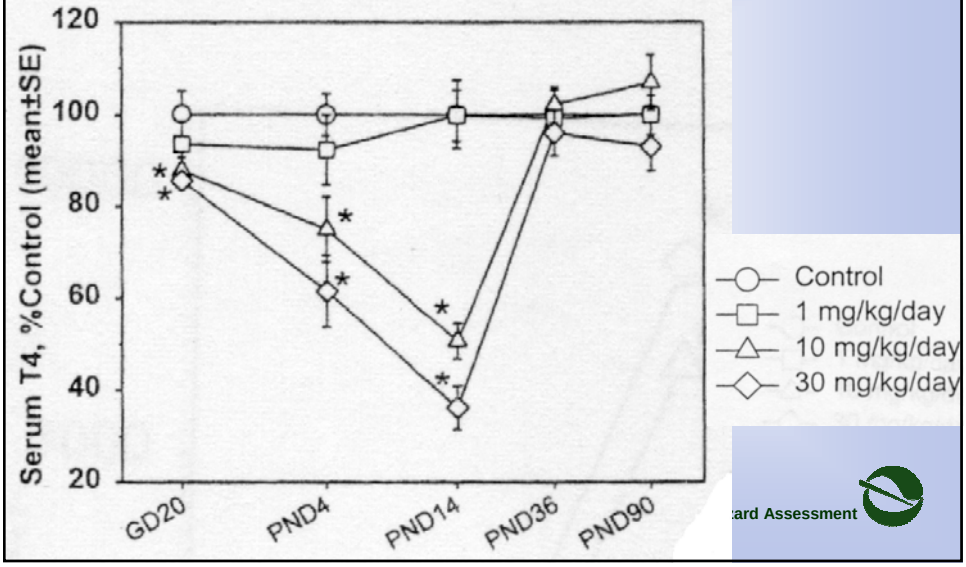
Thyroid Hormone Disruption

- **Good evidence in rats and mice**
- **Some evidence in humans**
- **Relative potencies**

  penta-BDE > octa-BDE >>> deca-BDE
- **Effects additive with co-exposures to PCBs**
- **Possible mechanisms**
  - Hormone mimicry (transthyretin binding)
  - UDGPT enzyme induction (↑ T4 excretion)

Example: Thyroid Hormone Disruption

•Zhou et al. (2002): Penta-BDE (tech.) given to pregnant rats 0, 1, 10, 30 mg/kg-d from gestational day 6 through postnatal day 21

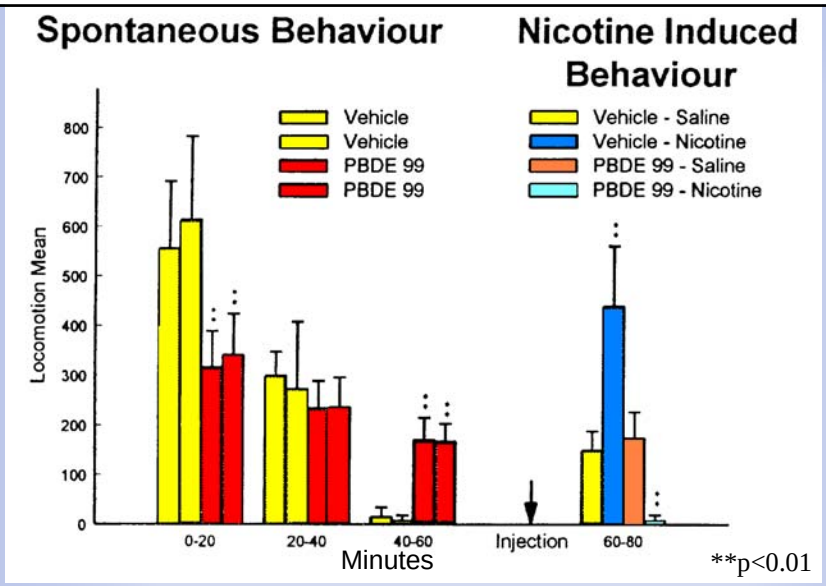


Estrogenic Effects

- **Postnatal exposure of rats to PBDE-99 altered expression of estrogen-regulated genes (Lichtensteiger *et al.*, 2003)**
  - Prostate: androgen receptor, estrogen receptor ER-α and ER-β, insulin-like growth factor (IGF-I)
  - Brain: Progesterone receptor, ER-α
- ***In vivo* estrogenic activity was not predicted from *in vitro* assays.**
  - PBDE-99 low estrogenic activity in MCF-7 cells.

Developmental Toxicity

- **Neurological system *(3 independent laboratories)***
  - **Altered behavior, learning and memory in mice**
  - **Hearing loss in rats**
  - **Effects permanent, i.e., measured in adulthood**
  - **Effects additive with co-exposure of PBDE and PCB**
- **Male reproductive system *(2 labs)*:**
  - **Delayed puberty**
  - **Increased ventral prostate and seminal vesicle weights**
- **Female reproductive system *(3 labs)*:**
  - **Delayed puberty**
  - **Alterations to ovary cell structure**



Effects, measured in adulthood, worsen with age.
Same pattern seen with many neurotoxic PCBs.

Viberg *et al.*, 2000

Risk:
Compare High-end Human Levels to Tissue Levels in PBDE-treated Rodents

- **Estimates of rodent body burdens of PBDE resulting from doses that caused these effects are equivalent to total PBDE levels attained in humans.**
  - If humans are as sensitive as animals, then there is:

"No margin of safety." Science News (2003) 164:266-8.

  - Better data are needed to compare tissue concentrations between rodents and humans.

Risk (continued)

- **An even greater concern: PBDEs and PCBs may be working together.**
  - PCB levels are usually higher than PBDEs
  - Same effects on some mechanistic endpoints
  - Co-administration of PCB and PBDE caused additive effects with respect to:
    - **behavior alterations in mice**
    - **thyroid hormone disruption**
  - PBDEs/PCB co-exposures further increases the likelihood that exposure will result in health effects.

Penta- and Octa-BDE are Now Banned Chemicals

- **Banned in California starting 2008**
  - AB302 (Chan et al.), signed into law in August.
- **U.S. manufacturer announced it will voluntarily cease production by end of 2004**
- **Banned by the European Union starting 2005**
- **Already voluntarily phased out in Japan**

Text of California Ban (AB302)

“ On and after January 1, 2008, a person may not manufacture, process, or distribute in commerce a product, or a flame-retarded part of a product, containing more than one-tenth of 1 percent of pentaBDE or octaBDE, by mass.”

Summary

- **PBDEs in consumer products are escaping into the environment – now everywhere**
- **PBDE levels rising rapidly in fish, other wildlife and people in North America**
- **Some folks have much higher levels than most for reasons unknown.**
  - Levels similar to levels associated with health effects
- **Penta- and Octa-PBDE banned in CA and the EU; not used in Japan.**
  - Renewed concern over Deca (new data on debromination by UV and biota)